REMARKS/ARGUMENTS

Claims 51-56, 58, 63-70 and 75 are cancelled without prejudice or disclaimer. The canceled claims are rewritten as new claims 79-94. The following table shows the correspondence of the new claims to the canceled claims:

New Claim	Support
79	51
80	52
81	53
82	54
83	55
84	56
85	57
86	63
87	64
88	65
89	66
90	67
91	68
92	69
93	70
94	75

Additionally, claims 79-81, 88-90 and 94 were amended to specify that the homology arms are larger than 20 kb. Support for this amendment is found at page 6, lines 6-8. Claims 79-81, 88-90 and 94 are further amended to clarify that the quantitative assay requires the use of a probe directed to the unmodified allele of the endogenous gene locus to detect reduced copy number of the unmodified allele compared to that of a reference gene in the cell from (b) thereby indicating modification of allele. Support for this amendment is found throughout the specification, including at page 31, lines 5-11. No new matter is added by the new claims and the Examiner is respectfully requested to enter this amendment.

I. Rejections under 35 USC § 102(b).

Claims 51-55, 57-63, 65-69, and 71-78 were rejected as anticipated by Kucherlapati et al. (WO 94/02602). Claims 51-55, 57-63, 65-69 and 77-78 are canceled. This rejection is respectfully traversed as it may be applied to new claims 79-83, 88-92 and 94.

The cited prior art reference does not describe (1) homologous recombination of large DNA vectors equivalent to a LTVEC (e.g., having homology arms that total greater than 20 kb), (2)

targeted integration, (3) modifying an endogenous gene locus with site specific recombination sites, (4) site specific recombination sites loxP, lox511 and lox2272, or (5) use of a quantitative assay with a probe directed to an unmodified allele of the endogenous gene locus to detect reduced copy number of the unmodified allele compared to that of a reference gene. Accordingly, applicants submit that the examiner has failed to establish a *prima facie* case of anticipation because the cited prior art reference fails to teach every limitation required by the claims. In light of the above amendments, it is respectfully requested that this rejection be withdrawn.

II. Rejections under 35 USC § 103(a).

A. Claims 51-63 and 65-78 were rejected as obvious in light of Kucherlapati et al. when taken with Yang et al. (1997) Nature Biotechnology 15:859-865. This rejection is respectfully traversed as it may be applied to new claims 79-87 and 89-94.

Obviousness is a legal conclusion based on underlying facts of four general types: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) any objective indicia of nonobviousness. See Graham v. John Deere Co., 383 U.S. 1, 17-18, 15 L. Ed. 2d 545, 86 S. Ct. 684 (1966); Continental Can Co. USA, Inc. v. Monsanto Co., 948 F.2d 1264, 1270, 20 USPQ2d 1746, 1750-51 (Fed. Cir. 1991); Panduit Corp. v. Dennison Mfg. Co., 810 F.2d 1561, 1566-68, 1 USPQ2d 1593, 1594 (Fed. Cir. 1987). Determination of obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention." ATD Corp. v. Lydall, Inc., 159 F.3d 534, 546, 48 USPQ2d 1321, 1329 (Fed. Cir. 1998). There must be a teaching or suggestion within the prior art, within the nature of the problem to be solved, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to particular sources, to select particular elements, and to combine them as combined by the inventor. See Ruiz v. A.B. Chance Co., 234 F.3d 654, 665, 57 USPQ2d 1161, 1167 (Fed. Cir. 2000); ATD Corp., 159 F.3d at 546, 48 USPQ2d at 1329; Heidelberger Druckmaschinen AG v. Hantscho Commercial Prods., Inc., 21 F.3d 1068, 1072, 30 USPQ2d 1377, 1379 (Fed. Cir. 1994) ("When the patented invention is made by combining known components to achieve a new system, the prior art must provide a suggestion or motivation to make such a combination.").

Kuncherlapati et al. Kuncherlapati et al, describe the introduction of standard targeting vectors (having homology arms less than 20 kb total) by homologous recombination or random integration of YACs, into ES cells.

Kuncherlapati et al. does not disclose or suggest (1) homologous recombination of large DNA vectors equivalent to a LTVEC (e.g., having homology arms that total greater than 20 kb), (2) targeted integration, (3) modifying an endogenous gene locus with site specific recombination sites, (4) site specific recombination sites loxP, lox511 and lox2272, or (5) use of a quantitative assay with a probe directed to an unmodified allele of the endogenous gene locus to detect reduced copy number of the unmodified allele compared to that of a reference gene.

Yang et al. as a whole. Yang, et al, describe the random integration of BAC-derived vectors into ES cells. The vectors are not introduced into ES cells by homologous recombination; rather, the BACs are modified by bacterial homologous recombination to create BAC-derived vectors. These vectors are randomly integrated into the ES cells.

Yang et al. does not disclose or suggest (1) targeted integration, (2) the use of site specific recombination sites, (3) recombination sites loxP, lox511 and lox2272, or (4) use of a quantitative assay with a probe directed to an unmodified allele of the endogenous gene locus to detect reduced copy number of the unmodified allele compared to that of a reference gene.

The analysis required by § 103(a). The above remarks are fully applicable to this rejection and are herein incorporated by reference. As shown by the above analysis, applicants respectfully submit that the examiner has failed to establish a *prima facie* case of obviousness because neither cited prior art reference, alone or in combination, suggest modifying an endogenous gene locus by methods which require (1) targeted integration, (2) the use of site specific recombination sites, (3) recombination sites loxP, lox511 and lox2272, or (4) use of a quantitative assay with a probe directed to an unmodified allele of the endogenous gene locus to detect reduced copy number of the unmodified allele compared to that of a reference gene. Thus, even combining the cited references does not lead one to the claimed method.

Accordingly, in light of the above remarks, it is respectfully requested that this rejection be withdrawn.

B. Claims 51-55, 57-69 and 71-78 were rejected as obvious in light of Kuncherlapati et al. when taken with Lie et al. (1998) Current Opinion Biotech 9:43-48. This rejection is respectfully traversed as it may be applied to new claims 79-83, 85-92 and 94. The instant invention and Kuncherlapati et al. are summarized above.

Lie et al. as a whole. Lie et al. summarizes advances in quantitative PCR technology, for example, the Taqman® technology to quantify the number of copies of a DNA template in a

genomic DNA sample.

Lie et al. do not disclose or suggest (1) methods of creating a modified endogenous gene locus flanked either downstream, upstream, or both sides by a site specific recombination site, (2) homologous recombination of large DNA vectors equivalent to a LTVEC; or (3) targeted integration of an LTVEC into a host genome.

The analysis required by § 103(a). The above remarks are fully applicable to this rejection and are herein incorporated by reference. As described above, Kuncherlapati et al. do not disclose or suggest (1) homologous recombination of large DNA vectors equivalent to a LTVEC (e.g., having homology arms that total greater than 20 kb), (2) targeted integration, (3) modifying an endogenous gene locus with site specific recombination sites, (4) site specific recombination sites loxP, lox511 and lox2272, or (5) use of a quantitative assay to detect a modified cell. Although the addition to Lie et al. addresses one of the missing elements, the combined references fail to teach the remaining missing elements.

Further, it is respectfully submitted that these references are not properly combinable because, as described above, Kuncherlapati et al. had no need to use a quantitative assay described by Lie et al. when using YACs, since he obtained random integration (see page 12, lines 25-29), and, when using targeting vectors, the homology arms were small enough for standard qualitative PCR or Southern blot analysis. Although Yie may discuss quantitative PCR, he provides no indication how this technique could be used or reason that it should be used in gene targeting in place of conventional methods such as qualitative PCR or Southern blot analysis. The strategy for using quantitative PCR in gene targeting (i.e., designing a probe to the unmodified allele) and advantages of so doing (e.g., detecting of larger insertions) are provided by the present application not the cited art. Thus, there is no suggestion or teaching within the prior art references for making the combination.

Accordingly, in light of the above remarks, it is respectfully submitted that this rejection be withdrawn.

Conclusion

It is believed that this document is fully responsive to the Final action dated 4 April 2006 and Advisory Action dated 29 July 2005. In light of the above amendments and remarks, it is believed that the claims are now in condition for allowance, and such action is respectfully urged.

Fees

The fee for filing of an RCE now due is $790. In addition, since the Final Rejection was issued 6 April 2005, a two month extension of time fee for $450 is required for the filing of this RCE to extend the response date to 6 September 2005. Accordingly, the Commissioner is hereby authorized to charge Depos Account Number 18-0650 in the amount of $1240, or any additional fees that may be determined to be du

Respectfully submitted

Valeta Gregg, Ph.D., Reg. No. 35,127
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, New York 10591
(914) 593-1077 (direct)